The basics of histamine biology

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Objective: To review the evolution of our understanding of the basics of histamine biology as it pertains to the treatment of allergic rhinitis.

Data Sources: Review articles and original research were retrieved from MEDLINE, OVID, PubMed (1950 to November 2009), personal files of articles, and bibliographies of located articles that addressed the topic of interest.

Study Selection: Key articles were selected that, taken together, provide a history of scientific insight into histamine biology and receptors and mechanism of action of antihistamines. Publications included reviews, treatment guidelines, and clinical studies (primarily randomized controlled trials) of both children and adults.

Results: The seminal work on histamine was published in 1910, but histamine was not identified as a mediator of anaphylactic reactions until 1932. Research later showed that histamine is a major mediator responsible for the symptoms of allergic rhinitis, with its activities mediated through 4 G protein–coupled receptors. Most of histamine's effects are exerted through the H_1 receptor, but some effects are through the H_2 and H_3 receptors, and possibly also through the H_4 receptor.

Conclusions: We hope that the progress made in understanding the mechanism of action of the histamine response will lead to better targeted treatment options.

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INTRODUCTION

This article reviews the science behind histamine and its receptors and the relation of histamine's activity to the symptoms of allergic rhinitis. How antihistamines are able to alleviate symptoms of allergic rhinitis is also discussed, including the advantages of intranasal administration of these compounds.

Although antihistamines have been in use for more than 60 years, and topical therapies of the respiratory tract have been used for centuries, it is only recently that intranasal antihistamines have begun to be more widely used as a treatment for allergic rhinitis. Intranasal antihistamines have been shown to have potent antihistamine effects, as well as other more broad-based anti-inflammatory activities.[1–3]

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EARLY SCIENTIFIC ADVANCES

In 1910, Dale and Laidlaw[4] discovered a substance that was capable of producing smooth muscle contraction in preparations of isolated guinea pig ileum. Later, in 1924, Lewis and Grant[5] demonstrated that this substance, H substance, could be released from the skin by antigen antibody interactions and found the substance to be β-aminoethylimidazole (also known as 2-[4-imidazolyl]-ethylamine). Three years later, Best and colleagues[6] found histamine in human tissue. In 1932, histamine was identified as a mediator of anaphylactic reactions.[7] Histamine has since been found to mediate numerous biological processes, both physiologic and pathologic, some of which are related to allergic rhinitis.

METABOLISM OF HISTAMINE

The metabolism of histamine mainly occurs via 2 enzymatic pathways, through the activities of histamine *N*-methyltransferase and diamine oxidase or histaminase (Fig 1).[8,9] Histamine is metabolized rapidly. Most histamine is metabolized through the histamine *N*-methyltransferase pathway, which is in the central nervous system (CNS), the intestinal smooth muscle, the mucosa of the small intestine, the liver, and the kidneys. The remaining histamine is metabolized through diamine oxidase, located in the small intestine mucosa, liver, kidneys, certain cells (eosinophils), placenta, and skin. The major metabolic product is *N*-methylimidazole acetic acid.

MECHANISM OF ANTIHISTAMINE ACTIVITY

Histamine is composed of an imidazole ring with an ethylamine side chain. It was previously thought that antihistamines that contained an ethylamine side chain (such as histamine)

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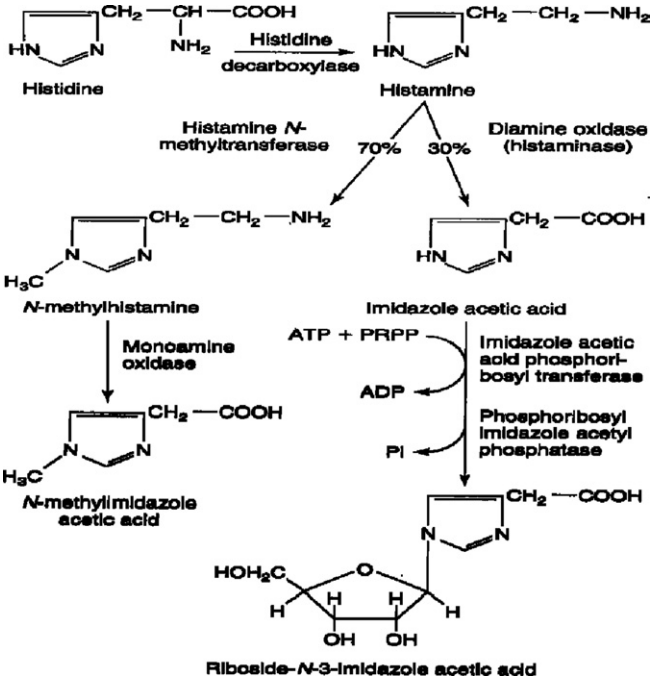

Figure 1. Metabolism of histamine.

behaved as competitive antagonists fitting into the histamine receptor in a lock-and-key fashion. Research has shown, however, that this concept is not valid because there are potent antihistamines without the ethylamine side chain that do not fit into the lock. We now know that the histamine receptors exist in inactive and active forms. Antihistamines are inverse agonists of histamine, causing the receptor to revert to its inactive state. The first use of an antihistamine in an animal model was reported in 1937. This was followed by the first clinically used antihistamine, pyrabenzamine, in 1942.[3] Soon after, multiple antihistamines (eg, diphenhydramine, tripelennamine, chlorpheniramine, and promethazine) were developed and began to be used widely in the treatment of allergic rhinitis. However, these early antihistamines had substantial adverse effects, including sedation. It was not until the 1990s that nonsedating oral antihistamines were introduced. They were followed by the introduction of intranasal antihistamines (eg, azelastine and olopatadine).

HISTAMINE AND ITS BIOLOGICAL EFFECTS

Histamine exerts its biological effects by binding to and activating 4 separate G protein–coupled receptors (GPCRs) (H_1, H_2, H_3, and H_4). GPCRs are the most common receptors for biological activity in the human body. GPCRs are 7-transmembrane chain receptors that mediate the activity of a tremendous number of molecules, including epinephrine, acetylcholine, histamine, and leukotrienes (Fig 2).

In the last decade, we have learned that the inactive and active forms of histamine exist in dynamic equilibrium. When histamine is added, it converts an inactive receptor to an active receptor. When antihistamines are added, they cause the opposite reaction. A drug does not have to fit into the receptor to cause the inactivity, it can do it as a steric reaction. Some of the larger effective drug moieties used now (too large to preclude entrance into the CNS) again do not have the ethylamine side chain.

The first 3 histamine receptors were discovered between 1966 and 1983; since 2000, the fourth receptor was discovered, and the scientific community has gained a better understanding of the histamine-receptor signaling process.[10]

The biological effects of histamine are protean (Fig 3).[9] Most of histamine's effects, related to allergic rhinitis, are mediated through the H_1 receptor, but some are through the H_2 and H_3 receptors and perhaps the H_4 receptor as well.

Acting via H_1, H_2, and H_3 receptors within the CNS, histamine also mediates wakefulness, alertness, and reaction time. Blocking histamine action within the CNS can, therefore, produce drowsiness and functional impairment with or without drowsiness.[11]

THE HISTAMINE RECEPTORS

H_1 Receptor

The H_1 receptor[3] is located on blood vessels and sensory nerves, which is important for rhinitis. The most important activities of the H_1 receptor are to increase vascular permeability, stimulate sensory nerves of airways, and promote chemotaxis of eosinophils. Therefore, it can cause sneezing, nasal congestion, and rhinorrhea. The H_1 receptor is the primary receptor responsible for the symptoms of rhinitis. H_1 antihistamines act as inverse agonists, causing a shift in

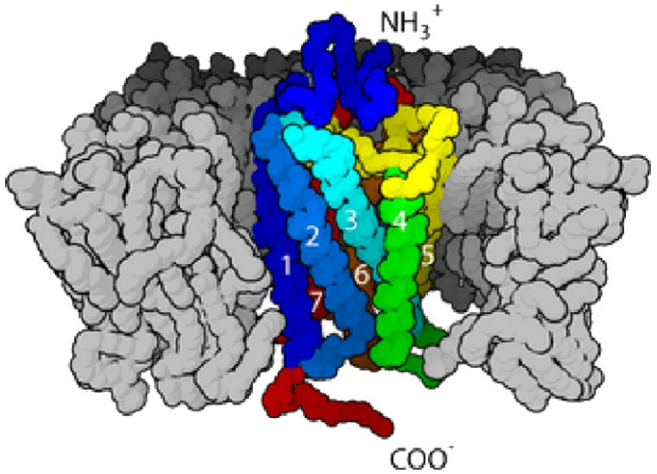

Figure 2. G protein-coupled receptors are 7-transmembrane chain receptors that mediate the activity of a tremendous number of molecules, including epinephrine, acetylcholine, histamine, and leukotrienes.

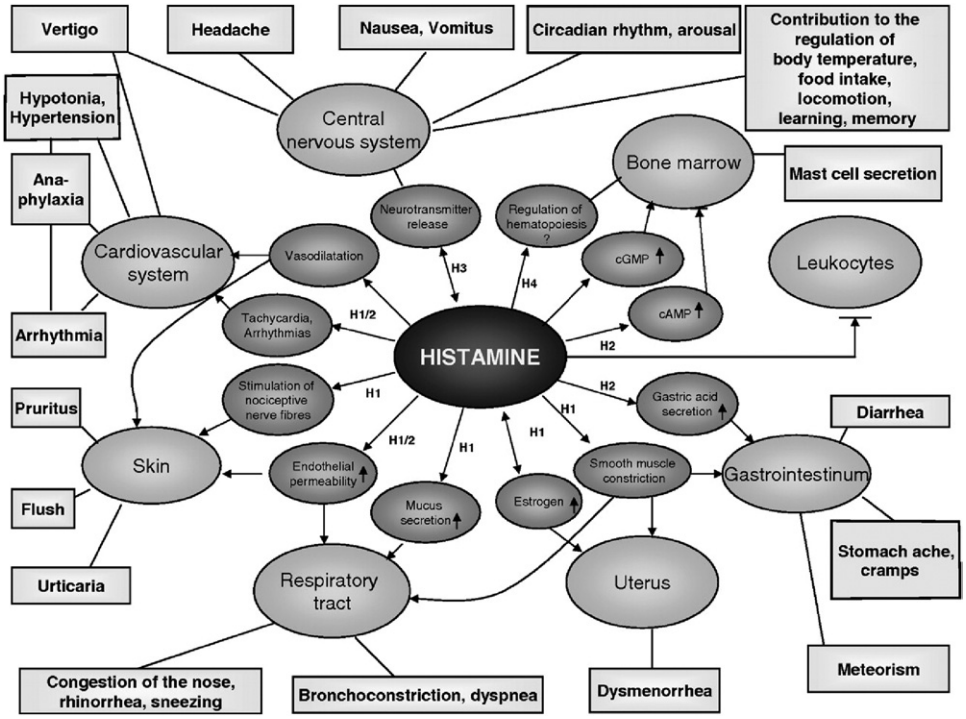

Figure 3. Summary of histamine-mediated symptoms. Reproduced with permission from Maintz et al.[9]

Table 1. Overview of 4 Histamine Receptors

Receptor	Location	Activities	Nasal symptoms produced
H_1	Blood vessels, sensory nerves (smooth muscle bronchi, GI tract, cardiac tissue, endothelium, CNS)	Increases vascular permeability, stimulation sensory nerves of airways, eosinophil chemotaxis, smooth muscle contraction in bronchi and GI tract, stimulation of vagal nerve receptors producing reflex smooth muscle contraction in airways, decreased AV node conduction time, enhancement of release of histamine and arachidonic acid derivatives, nitric oxide formation	Sneezing, itching, rhinorrhea, and perhaps some degree of nasal congestion via increased vascular permeability with leakage of fluid into the tissues and vasodilatation
H_2[16]	Vascular bed, epithelium of mucosa of nose, submucosal glands in nose, mucosa of stomach, CNS, cardiac tissue, uterus, smooth muscle	Stimulate mucous glands in airways, increases vascular permeability, direct chronotropic effect on atrium and inotropic action on ventricle, relaxation of esophageal sphincter, stimulation of suppressor T cells, decrease in neutrophil and basophil chemotaxis and activation, proliferation of lymphocytes, activity of NK cells	Potentially increase nasal airway swelling, producing nasal decongestion and perhaps increasing rhinorrhea
H_3[17,18,20]	Presynaptic nerves in the peripheral sympathetic adrenergic system, nasal submucosal glands, CNS (histaminergic nerves), airways, GI tract	Suppression of norepinephrine release at presynaptic nerve endings, stimulates nasal submucosal gland secretion, opposes bronchoconstriction and gastric acid	Can produce nasal congestion by prevention of norepinephrine after synaptic release
H_4[19]	Eosinophils, mast cells, basophils neutrophils, nasal turbinates (nerves), lung colon, epicanthus, bone marrow, spleen, liver	Chemotaxis and chemokinesis of mast cells and eosinophils, enhancement of the activity of other chemoattractants (eg, chemokines) on eosinophils, upregulation of adhesion molecules	Could enhance the inflammatory response to nasal allergen exposure

Abbreviations: AV, atrioventricular; CNS, central nervous system; GI, gastrointestinal; NK, natural killer.

equilibrium of the H_1 receptor to the inactivated state when bound to the H_1 antihistamine.[12] A summary of the activities of the H_1 receptor is given in Table 1.

H_2 Receptor

The H_2 receptor has always been thought of as a receptor for gastric acid, which is likely its major activity. However, it is located on the vascular bed, and it is known that to block all the systemic activities of histamine, you need a combination of both H_1 and H_2 antihistamines.[13–15] The H_2 receptor is also present in the epithelium of the mucosa of the nose, as well as the submucosal glands. Stimulation of the H_2 receptor produces glandular secretions. Activation of the H_2 receptor also likely contributes to the increased vascular permeability prompted by H_1 receptor stimulation. Thus, a combination of H_1 and H_2 receptor activation can contribute to nasal airway swelling and rhinorrhea. In a small intranasal allergen challenge, 15 asymptomatic humans were pretreated intranasally with H_1 antihistamine (levocabastine), H_2 antihistamine (ranitidine), or a combination of the 2 antihistamines. The H_1 and H_2 antihistamines were found to significantly reduce rhinorrhea and provided a diminished reduction of nasal blood flow due to allergen. The H_1 antihistamine significantly reduced sneezing, whereas the H_2 antihistamine alone did not.[16]

H_3 Receptor

In regard to rhinitis, the importance of the H_3 receptor is likely because it is expressed on presynaptic nerves in the peripheral sympathetic adrenergic system and also on the nasal submucosal glands. Stimulation of the H_3 receptor causes suppression of norepinephrine release at presynaptic nerve endings and stimulates nasal submucosal gland secretion.[17] In keeping with these biological activities, using a cat model of rhinitis, it was found that H_3 blockade enhanced the decongestant effect of an H_1 antihistamine.[18] Further activities of the H_3 receptor are listed in Table 1.

H_4 Receptor

The H_4 receptor can be found on eosinophils, mast cells, basophils, neutrophils, and nerves in the nasal turbinates. It is also seen in the lung, colon, epicanthus, bone marrow, spleen, and liver.[19] Activation of the H_4 receptor can enhance chemotaxis and chemokinesis of mast cells and eosinophils. Thus, H_4 receptor stimulation could theoretically enhance the inflammatory activity seen in allergic rhinitis.

CONCLUSION

Histamine is a major mediator responsible for the symptoms of allergic rhinitis. All of its activities are through 4 GPCRs. Most of its effects are exerted via the H_1 receptor, but some probably are also through the H_2 and H_3 receptors and perhaps the H_4 receptor. It is hoped that the progress made in understanding the mechanism of action of the histamine response will lead to better targeted treatment options.

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